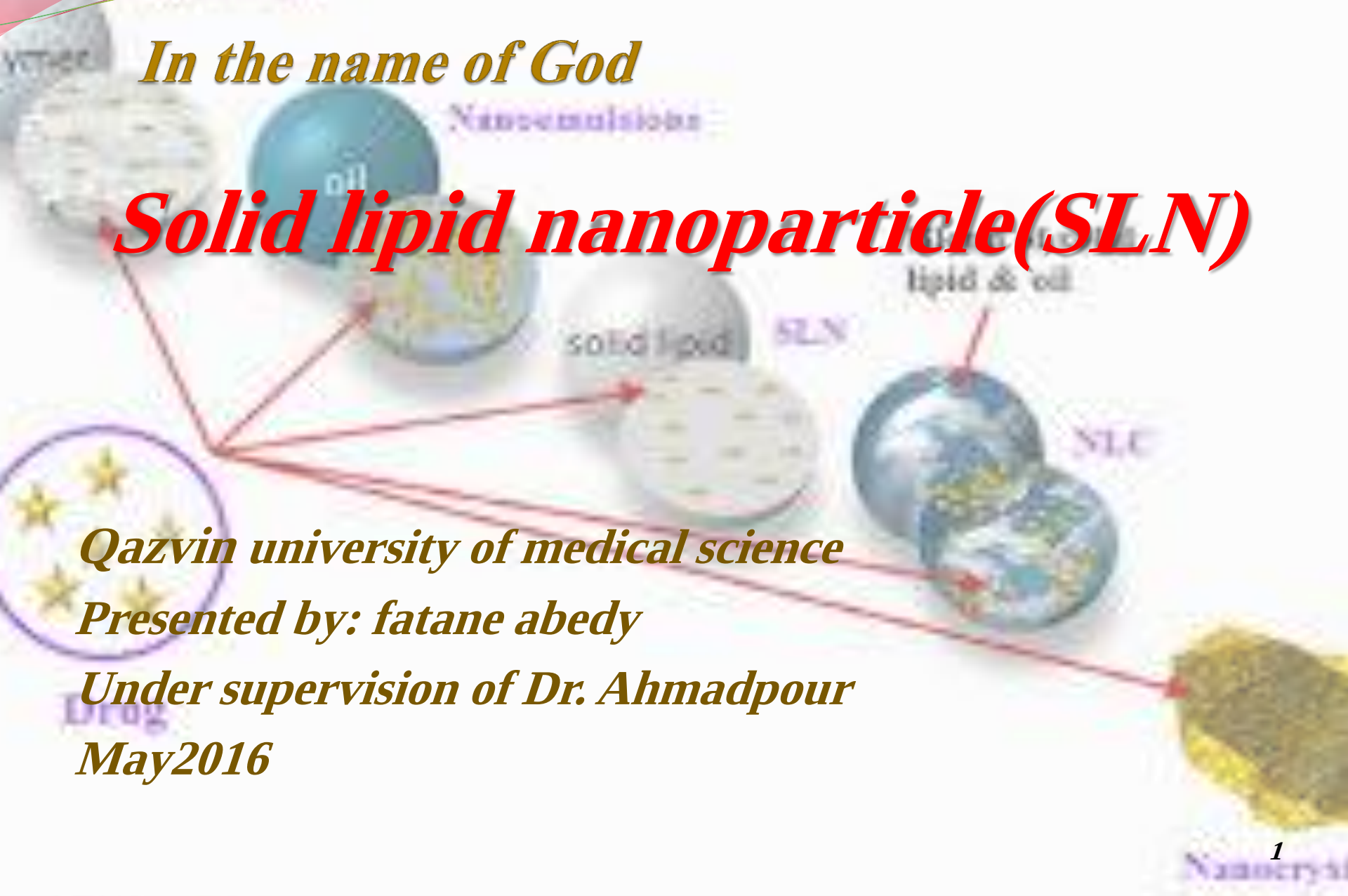
In the name of God

Solid lipid nanoparticle(SLN)



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Content:

- *Introduction*
- *History*
- *Process of production SLN*
  - *General ingredients*
  - *SLN preparation*
- *Characterize SLN*
- *Application of SLN*
- *Toxicity accept of SLN*
- *In vivo fate*
- *Reference*

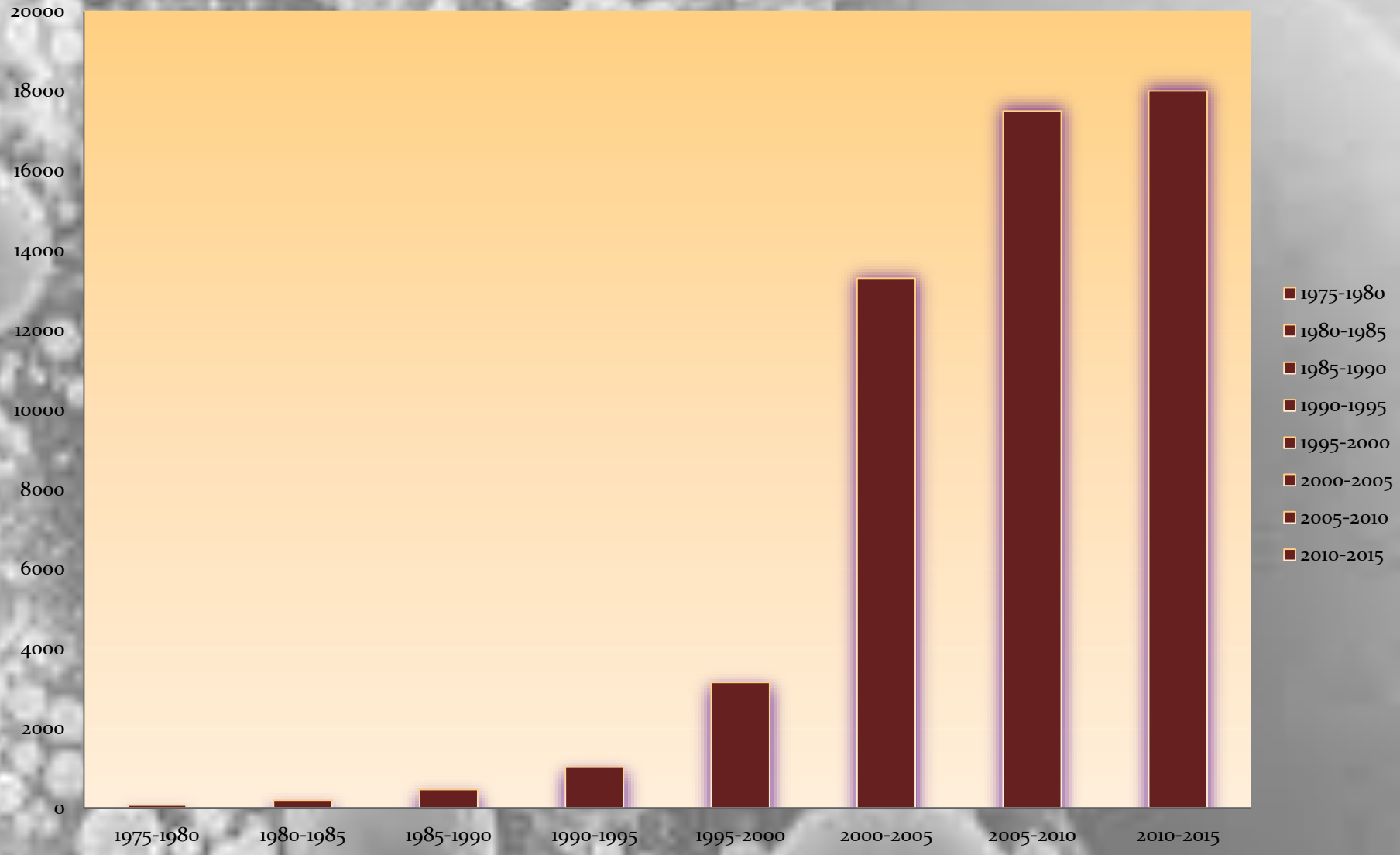
Introduction

- *made up of physiological lipids or synthetic*
- *SLN : 50-1000 nm*
- *first introduced by Muller et al in 1991*
- *Therapeutic , cosmetic and dermal, diagnostic application*
- *Last few years as colloidal drug carriers*
- *Several advantage ,minimize disadvantage*

History:

- ***Solid lipid used for several in form of pellet in peroral administration***
- ***Speicer and coworker (1980) : solid lipid microparticle with high speed mixer***
- ***Muller et al (1991):submicron size of solid lipid with High pressure homogenization(SLN)***

TREND OF NANOPARTICLE



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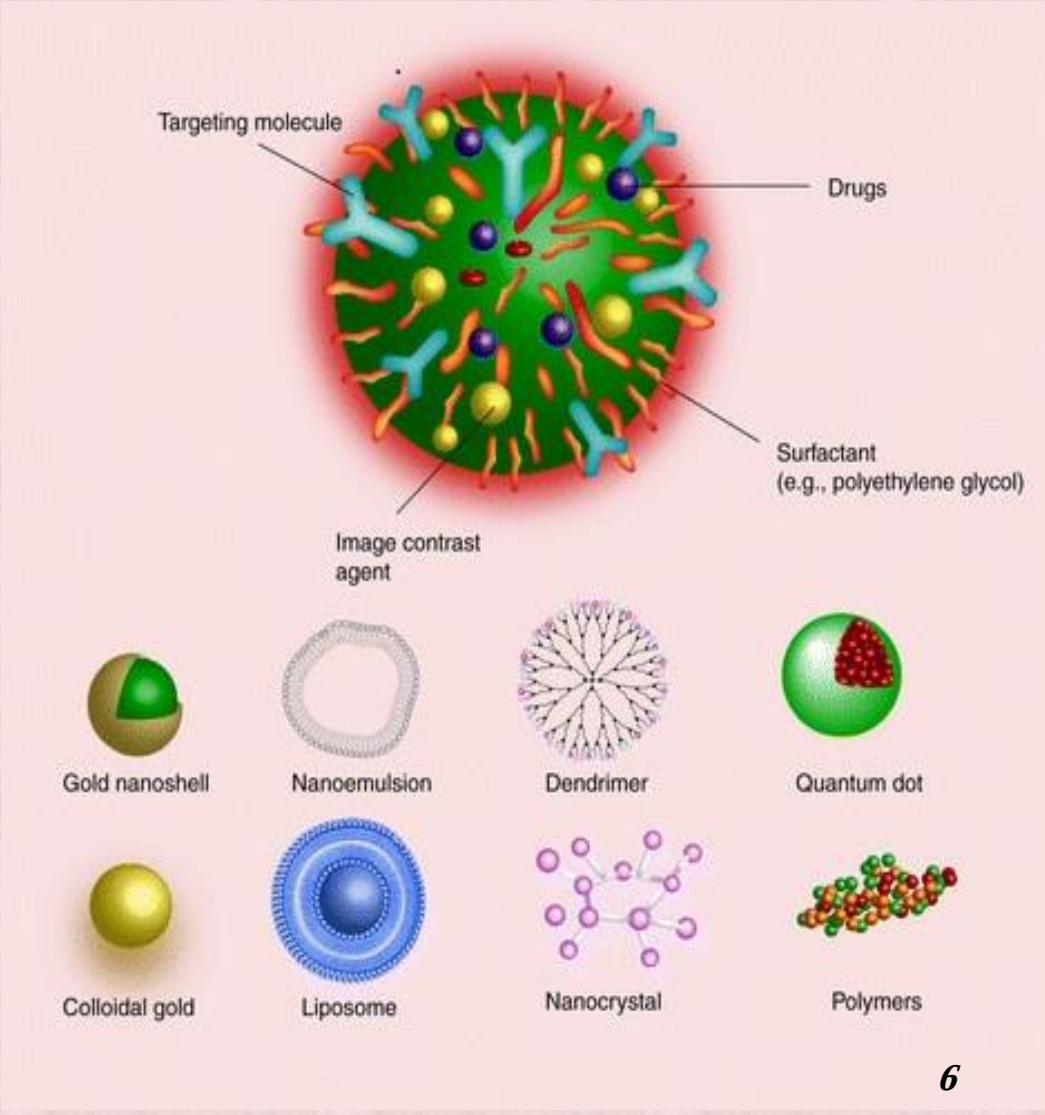
Colloidal carrier:

- ***Lipid emulsion***
- ***Liposome***
- ***Polymeric nanoparticle***



advantages include:

- *controlled drug release*
- *less toxic*
- *Protecting the labile and sensitive drugs from degradation*
- *ease of scale-up*
- *Low cost*
- *physical stability*
- *lipophilic and hydrophilic compounds can be delivered by SLN*
- *biodegradable*
- *different administration routes*

Challenge(1):

- ***Entrapment of water soluble drugs***

  Polymeric Lipid Hybrid Nanoparticles (PLN)

- ***Avoidance of Reticulo Endothelial System(RES)***

  coating with PEG,POLOXAMINE

  `Stealth particle`

- ***Controlled release of drug:***

  Nanostructured Lipid Carriers (NLC)

GENERAL INGREDIENTS(2):

- ***Solid lipid***

  triglycerides, partial glycerids

  fatty acids, steroids ,waxes

  physiological lipids decreases the danger

  of acute and chronic toxicity.

- ***Emulsifier***

  used to stabilize the lipid dispersion

  prevent particle agglomeration

- ***water***

Lipids and emulsifiers used for SLN

Lipids
Triglycerides
Tricaprin
Trilaurin
Trimyristin
Tripalmitin
Tristearin
Hydrogenated coco-glycerides (Softisan® 142)
Hard fat types
Witepsol® W 35
Witepsol® H 35
Witepsol® H 42
Witepsol® E 85
Glyceryl monostearate (Imwitor®900)
Glyceryl behenate (Compritol® 888 ATO)
Glyceryl palmitostearate (Precirol® ATO 5)
Cetyl palmitate
Stearic acid
Palmitic acid
Decanoic acid
Behenic acid
Acidan N12

Emulsifiers/Coemulsifiers
Soybean lecithin (Lipoid® S 75, Lipoid® S 100)
Egg lecithin (Lipoid® E 80)
Phosphatidylcholine (Epikuron® 170, Epikuron 200)
Poloxamer 188
Poloxamer 182
Poloxamer 407
Poloxamine 908
Tyloxapol
Polysorbate 20
Polysorbate 60
Polysorbate 80
Sodium cholate
Sodium glycocholate
Taurocholic acid sodium salt
Taurodeoxycholic acid sodium salt
Butanol
Butyric acid
Dioctyl sodium sulfosuccinate
Monooctylphosphoric acid sodium

W. Mehnert, K. Ma¨der / Advanced Drug Delivery Reviews 47 (2001) 165 –196

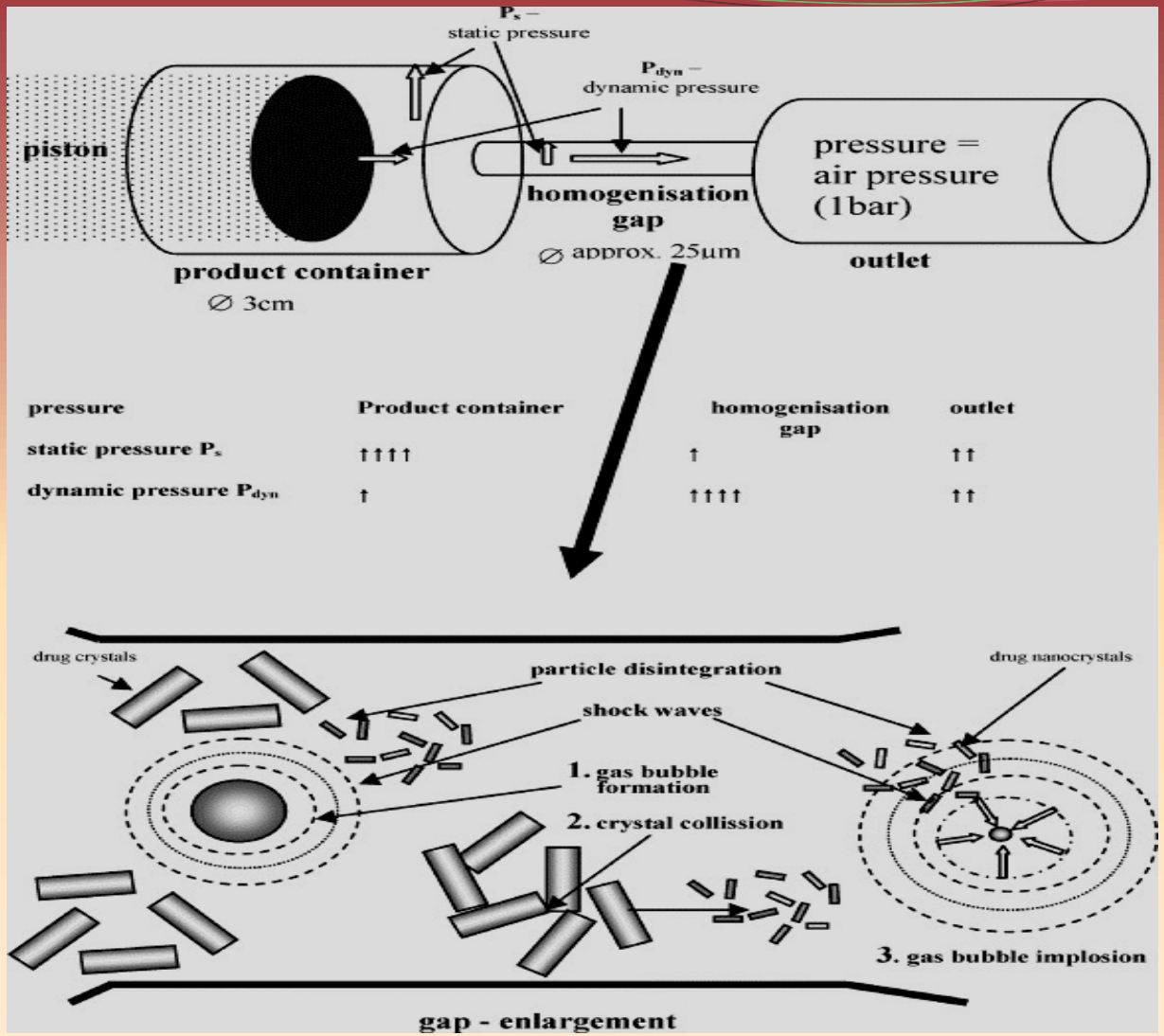
SLN Production(3):

- **SLN can be produced by various techniques:**

  - **High pressure homogenization**
  - **High shear homogenization and ultrasound**
  - **Microemulsion based SLN preparations**
  - **Supercritical Fluid technology**

High pressure homogenization:

- *Powerful technique*
- *pushes the liquid with high pressure (100-2000 bar) through a narrow gap ranging a few microns.*
- *The fluid accelerates to a very high viscosity of over 1000 km/h.*
- *Very high shear stress and cavitation forces disrupt the particles down to submicron range.*
- *5% - 40%: lipid content*



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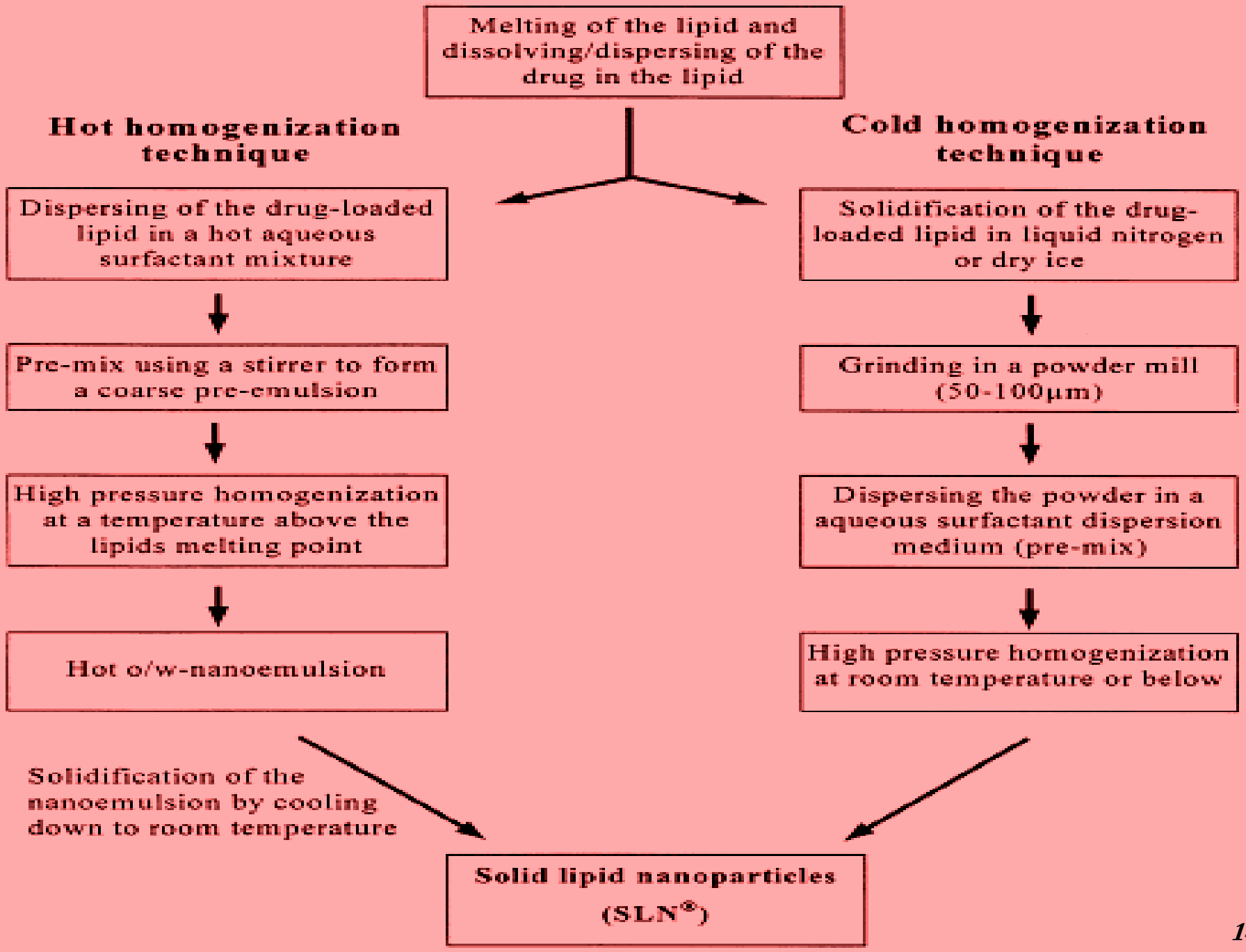
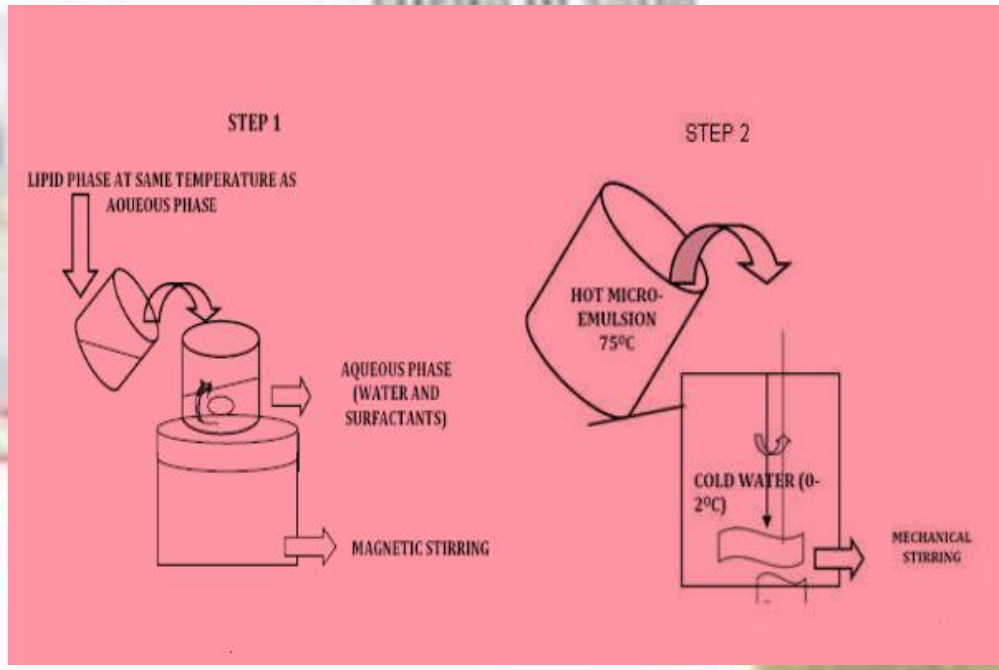

Melting of the lipid and dissolving/dispersing of the drug in the lipid
Hot homogenization technique
Dispersing of the drug-loaded lipid in a hot aqueous surfactant mixture
Pre-mix using a stirrer to form a coarse pre-emulsion
High pressure homogenization at a temperature above the lipids melting point
Hot o/w-nanoemulsion
Cold homogenization technique
Solidification of the drug-loaded lipid in liquid nitrogen or dry ice
Grinding in a powder mill (50-100µm)
Dispersing the powder in a aqueous surfactant dispersion medium (pre-mix)
High pressure homogenization at room temperature or below
Solidification of the nanoemulsion by cooling down to room temperature
Solid lipid nanoparticles (SLN®)

Ultrasonication:

- ***high speed homogenization***
- ***Initially techniques***
- ***advantage :equipment used is commonly available***
- ***problems: broader size***
  metal contaminations
  physical instability

Microemulsion based SLN preparation

- *dilution of microemulsions*
- *The hot microemulsion is dispersed in cold water (2-3°C) under stirring.*
- *Lipid content are lower compare with the HPH*



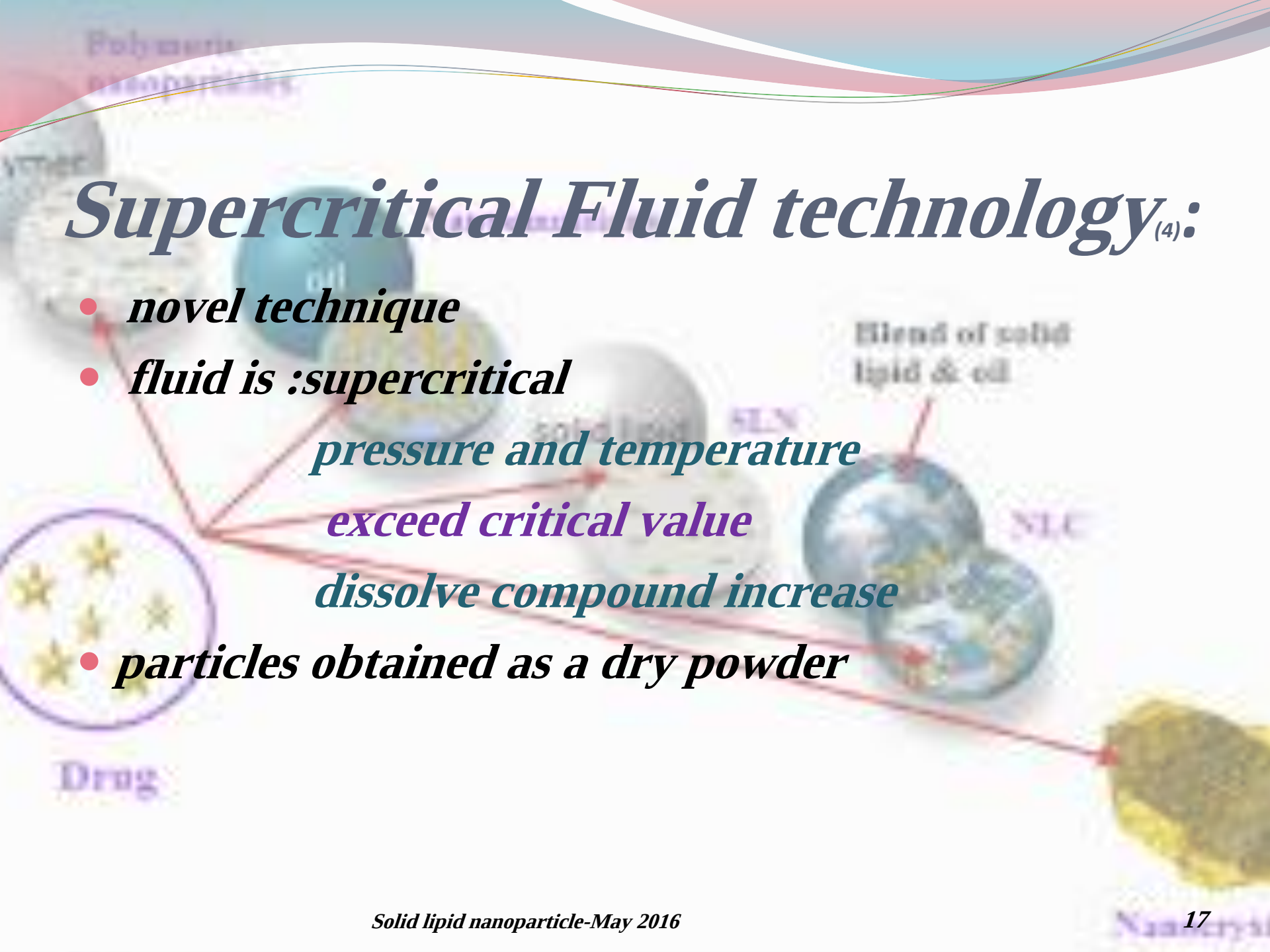
Supercritical Fluid technology(4):

- *novel technique*
- *fluid is :supercritical*

  pressure and temperature

  exceed critical value

  dissolve compound increase
- *particles obtained as a dry powder*



	advantage	disadvantage
Hot homogenization	*Smaller particle*	*• temperature induce drug degradation* *• complexity of the crystallization*
cold homogenization		*Larger particle sizes*
Ultrasonication (high speed homogenization)	*• Equipment used is very common* *• No temperature induced drug degradation*	*• Potential metal contamination* *• Broader particle size*
Micro emulsion based SLN preparations	*Solvent less processing*	*Lipid content are lower*
Supercritical Fluid technology	*dry powder* *Mild pressure and*	*More expansive*

Sterilization:

- ***Parenteral administration***
- ***Autoclave: heat resistant drug***
- ***Filtration: particle size below 200nm***
- ***gamma irradiation***

Drug release from SLN(5)

- ***drug in the outer shell and on the particle surface: released in the form of a burst***
- ***The drug incorporated into the particle core :released in a prolonged way.***

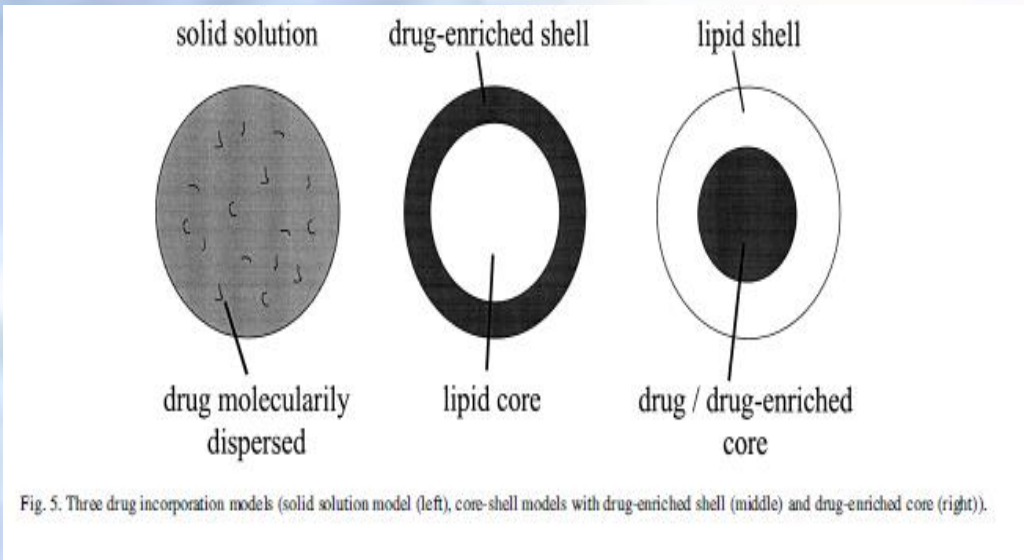
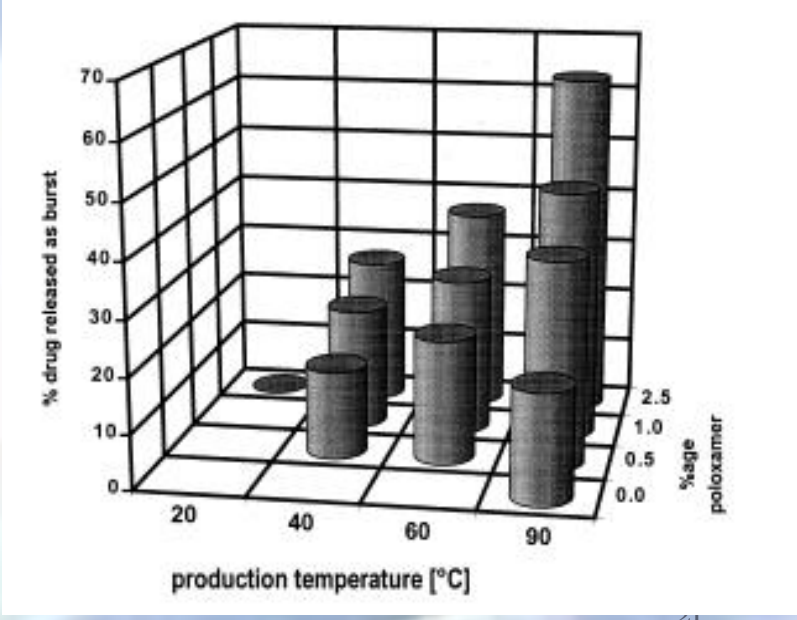


Fig. 5. Three drug incorporation models (solid solution model (left), core-shell models with drug-enriched shell (middle) and drug-enriched core (right)).

Drug release from SLN

- ***Higher temperatures and higher surfactant concentrations: increase the burst***
- ***SLN can be produced surfactant free or using surfactants which are not able to solubilizethe drug: avoid or minimize the burst***



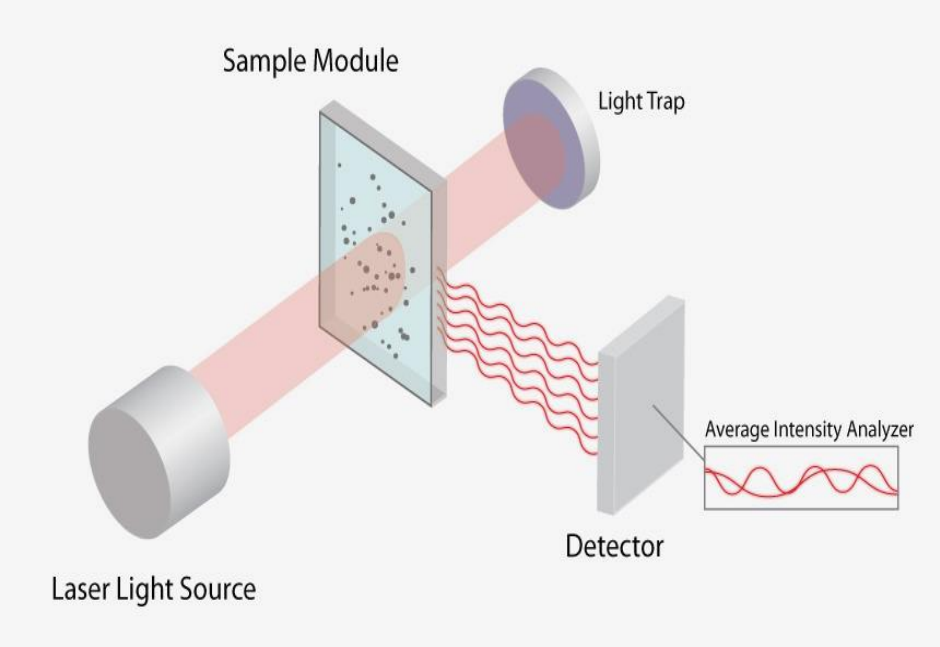
CHARACTERIZATION OF SLN(6):

important parameters :

- ***particle size and zeta potential***
- ***degree of crystallintity and lipid modification***
- ***coexistence of additional colloidal structures***

Particle size:

- *Photon correlation spectroscopy (PCS)*



- *dynamic light scattering*
- *detects size range of 3nm to 3µm*
- *good tool to characterize nano-particles*
- *fluctuation of the intensity of the scattered light which is caused by particle movement*

Particle size:

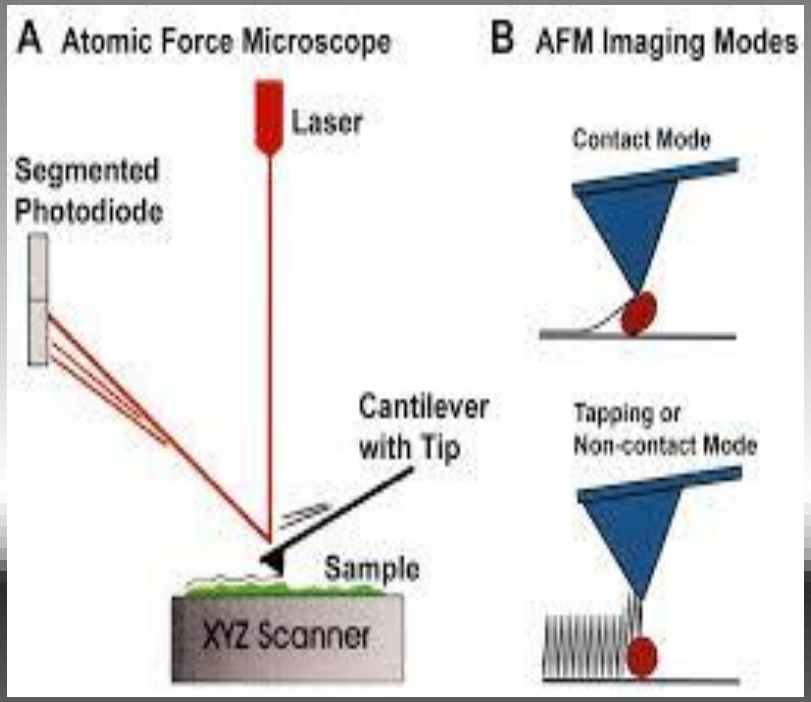
- *laser diffraction (LD)*

- *diffraction angle on the particle radius*
- *Detect size range of 100 nm to 180 µm.*
- *detection of larger microparticle*
- *recommended to use PCS and LD simultaneously*

Morphological structure:

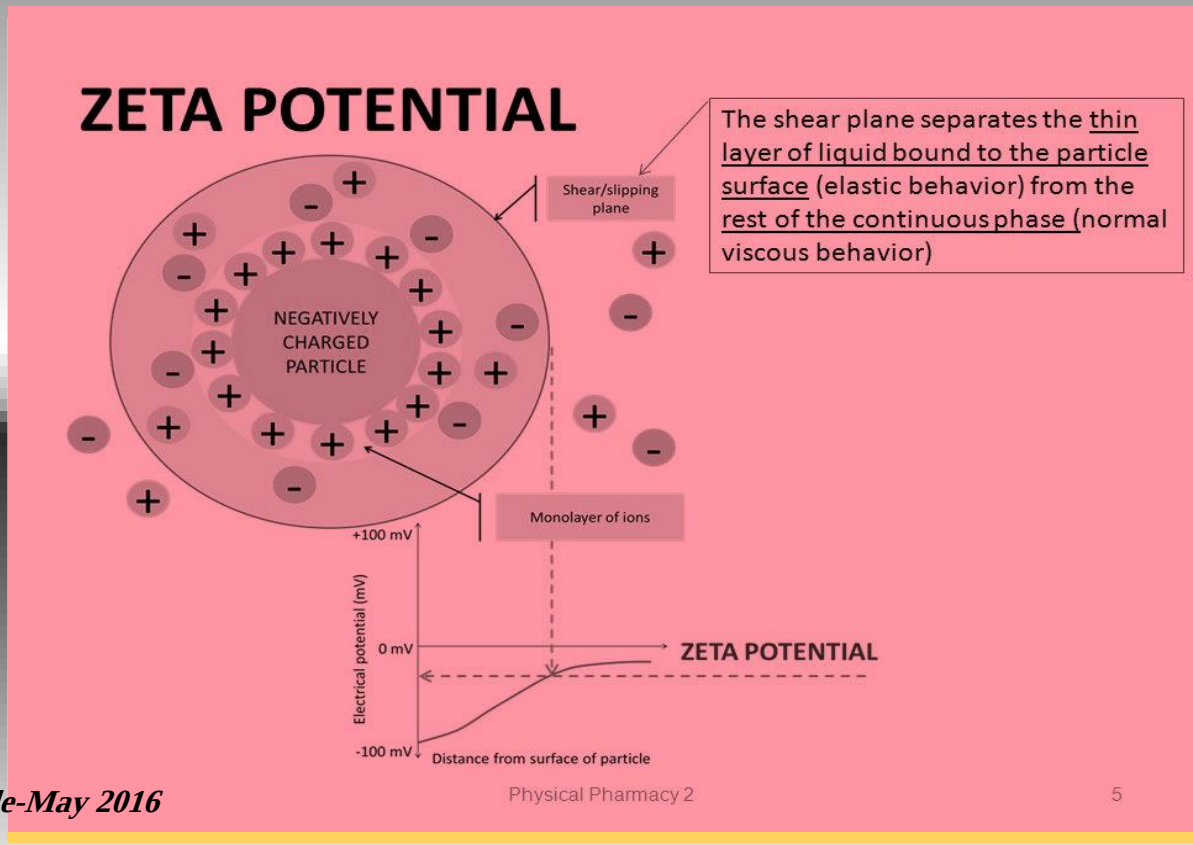
- *Atomic force microscopy (AFM)*

- ***Obtains image quickly***
- ***Observation of in situ***



Zeta potential :

zeta potential analyzer or zetameter.

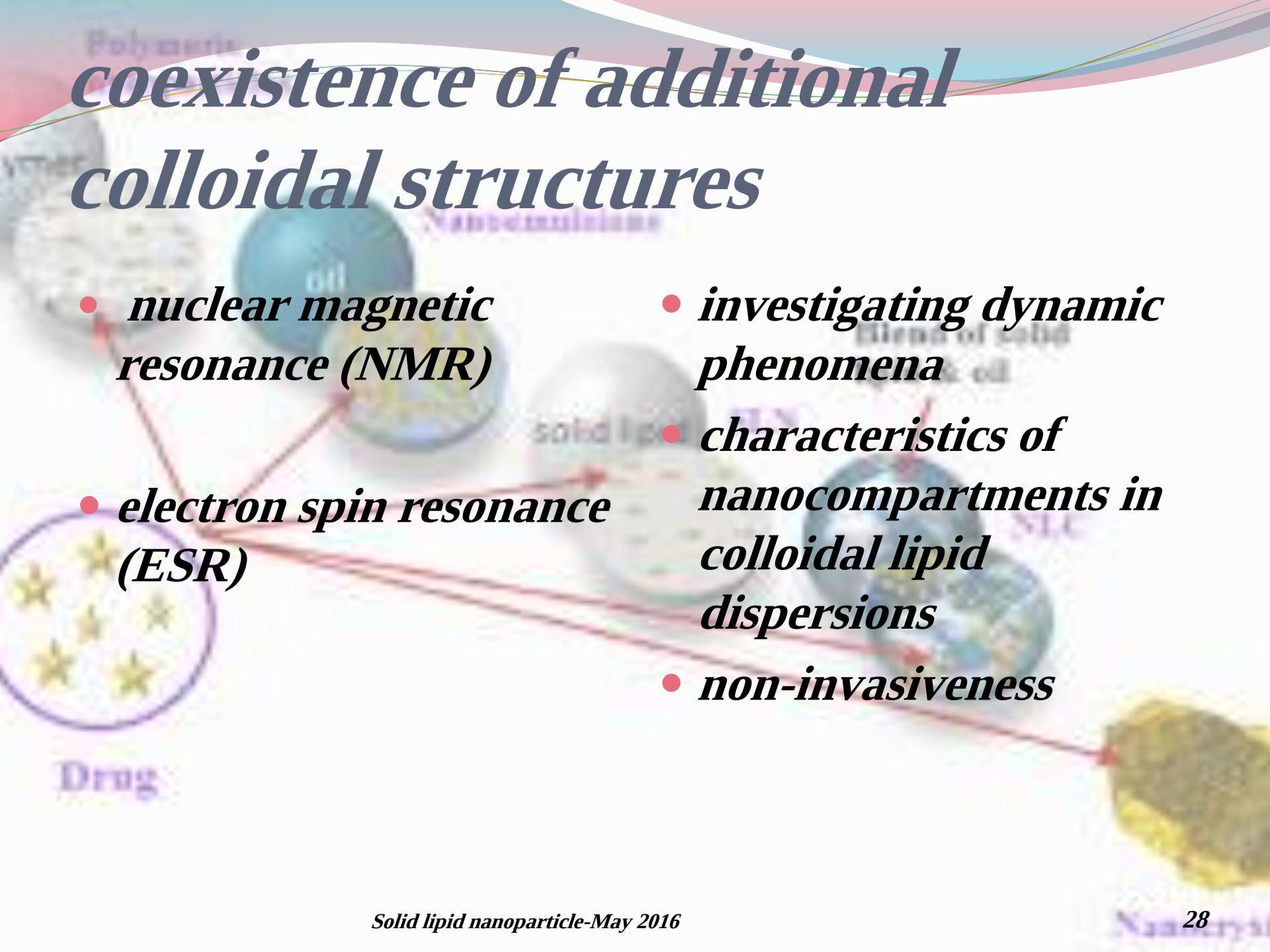


Measurement of crystallinity, lipid modification:

- ***related with drug incorporation and release rates***
- ***Differential scanning calorimetry (DSC)***
- ***X-ray scattering***
- ***Infrared and Raman spectroscopy***

coexistence of additional colloidal structures

- *nuclear magnetic resonance (NMR)*
- *electron spin resonance (ESR)*
- *investigating dynamic phenomena*
- *characteristics of nanocompartments in colloidal lipid dispersions*
- *non-invasiveness*



Application:

- ***Drug loader***
- ***A novel carrier for chemotherapy:***
  - ***cancer***
  - ***parasitic infections***
  - ***tuberculosis***
- ***potential new adjuvant for vaccines***
- ***gene therapy***
- ***central nervous system diseases***
- ***SLNs as cosmeceuticals***
- ***potential agriculture application***

Drug loader (7-8):

- ***Many different drugs incorporated in SLN***

- ***important point:*** ***loading capacity***

- ***solubility of drug in melted lipid***
- ***miscibility of drug melt and lipid melt***
- ***chemical and physical structure of solid lipid matrix***

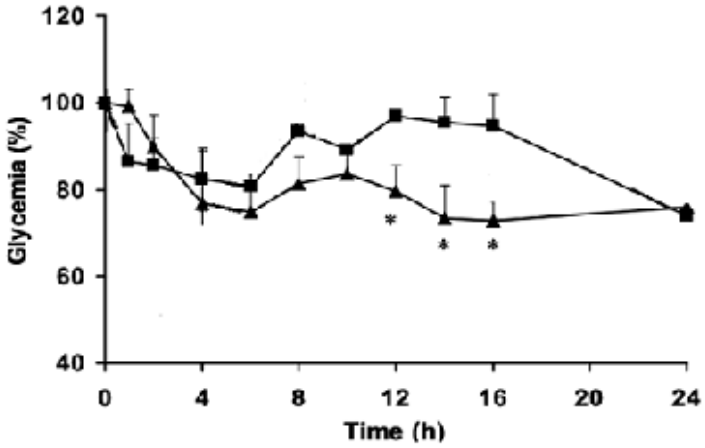


Table 1: A list of drugs and polymers used for the preparation of SLNs

Drug	Polymer	Method of preparation
Olanzapine	Hydrogenated soyaphosphatidylcholine	Modified high pressure homogenization
Rizatriptan	Tristearin,Phospholipon80	Modified solvent injection method
Alendronate NP	PLGA,Ethyl acetate, PF68	Double emulsion solvent diffusion
Clozapine Tetracaine, Etomidate, Prednisolone	Dynasan114,116, Tristearin,Dynasan112, Campritol 888ATO, Lipoid S75	Hot homogenization
Vitamin A Retinol	Compritol 888ATO, Miglyol 812, Dynasan 116	Hot homogenization
Gatifloxacin	Chitosan, Na alginate	Modified Coacervation
Insulin	PEG'Glycolgrafted chitosan	Ionic gelation
Paclitaxel	Tripalmitin, phosphatidylcholine	Microemulsion
Insulin	Hydrophobized cholesterol bearing pullulan	Ultra sonication
Mitoxantrone	Glyceryl behenate, Campritol 888ATO, lecithin	
Vinpocetine	Glyceryl monostearate,DCM, soyalecithin	Ultrasonic solvent emulsification
Insulin	Cetyl palmitate	Solvent emulsification evaporation
5-Fluorouracil	Dynasan 114,118, triglyceride, soyalecithin	Double emulsion Solvent evaporation
Methotrexate	Cetyl alcohol, Campritol 888 ATO,Tween 80	Microemulsion congealing technique
Gatifloxacin	Sodium alginate, Chitosan	Modified coacervation

http://www.banglajol.info/index.php/ICPJ/article/view/12065

CHEMOTHERAPY[9]*:*

CONVENTIONAL

- ***Poor specificity***
- ***Side effect***
- ***Drug resistance***

SLN

- ***enhanced permeability and retention(EPR)***
- ***Active tumor targeting***
- ***Encapsulation of chemotherapeutic drug***

SLN in tubercular chemotherapy:

- *Anti tubercular drug(ATD)*
- *Oral administration*
- *Detected in plasma 8 days*
- *Drug Concentration Above or Minimum inhibitory concentration(MIC90)*

SLN in the parasitic chemotherapy:

- ***Malaria***
- ***Leishmaniasis***
- ***Tryanosomiasis***

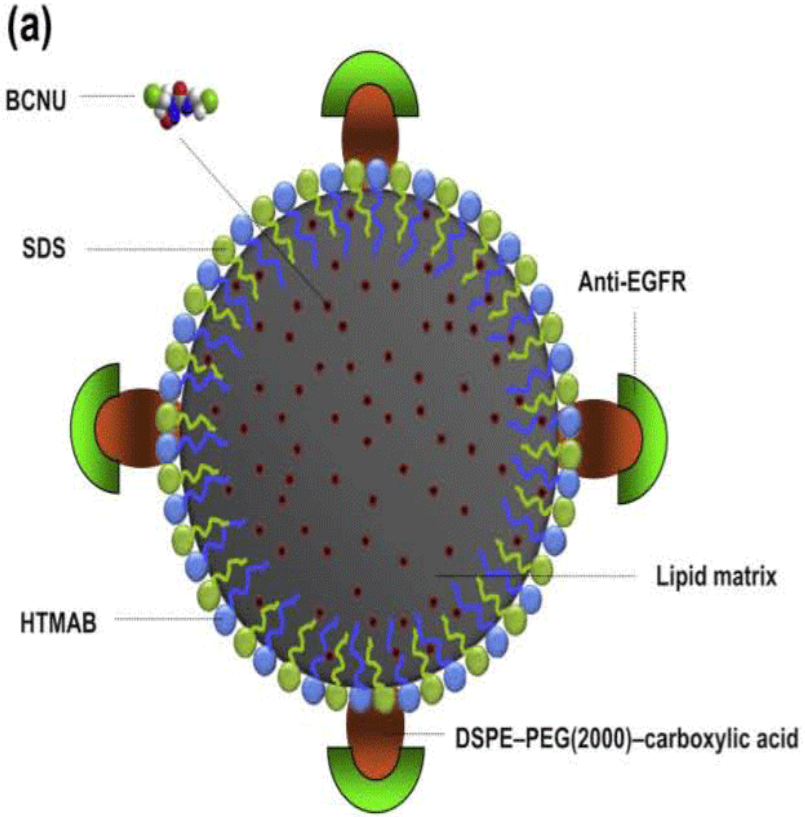
- ***Brain targeting by SLN***
- ***Administered intravenously***
- ***Enhanced uptake***
- ***Higher concentration in serum***

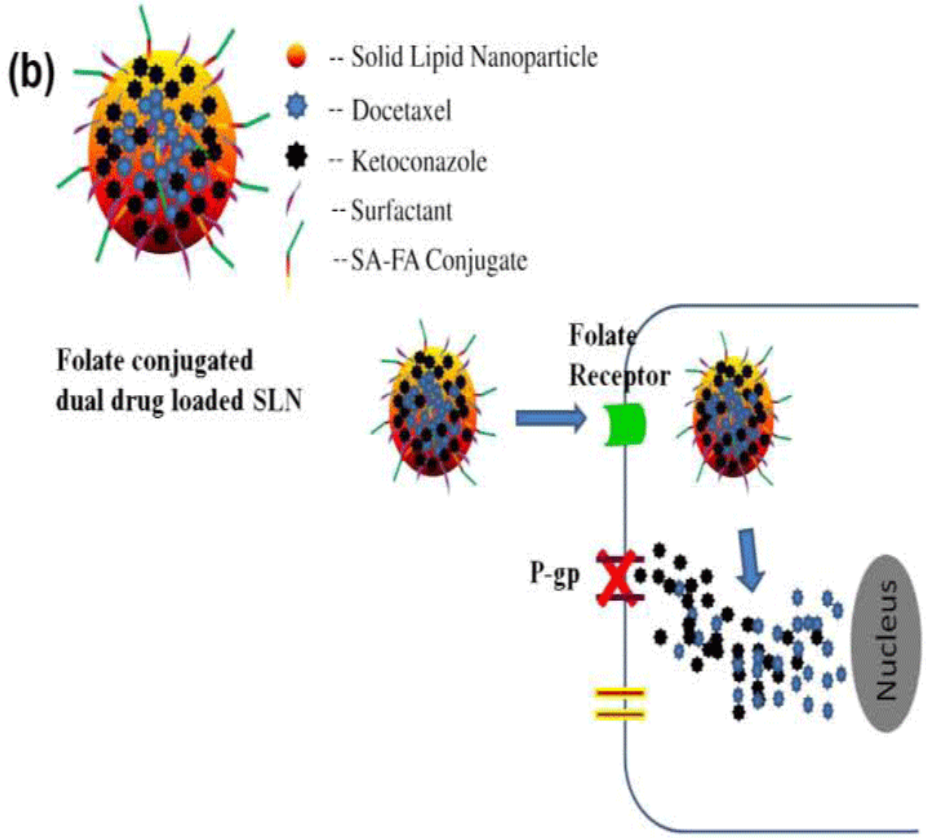
SLN in cancer chemotherapy:

- *first in-vivo studies*
- *Yang et al in 1999*
- *Camptothecin is an anticancer*
- *camptothecin-SLN(CA-SLN)*
- *increased accumulation of CA-SLN in brain, heart and RES organs*

- *Oyewumi et al*
- *PEG and folate coated SLN of gadolinium*
- *Increased cellular uptake and retention in cancer cell*

- *Bondi et al*
- *prepared NLC of anticancer drug temozolamide*
- *increase in the effect on human hepatocellular carcinoma cell line*


(a)
BCNU
SDS
Anti-EGFR
Lipid matrix
HTMAB
DSPE–PEG(2000)–carboxylic acid


(b)
-- Solid Lipid Nanoparticle
-- Docetaxel
-- Ketoconazole
-- Surfactant
-- SA-FA Conjugate
Folate conjugated
dual drug loaded SLN
Folate
Receptor
P-gp
Nucleus

new adjuvant for vaccines(10):

- ***Adjuvant are used in vaccination***
- ***enhance the immune response.***
- ***Freund's complete adjuvant (FCA) and Freund's incomplete adjuvant (FIA)***
- ***SLN: degraded more slowly***
  lasting exposure to the immune system
  good tolerability by the body.

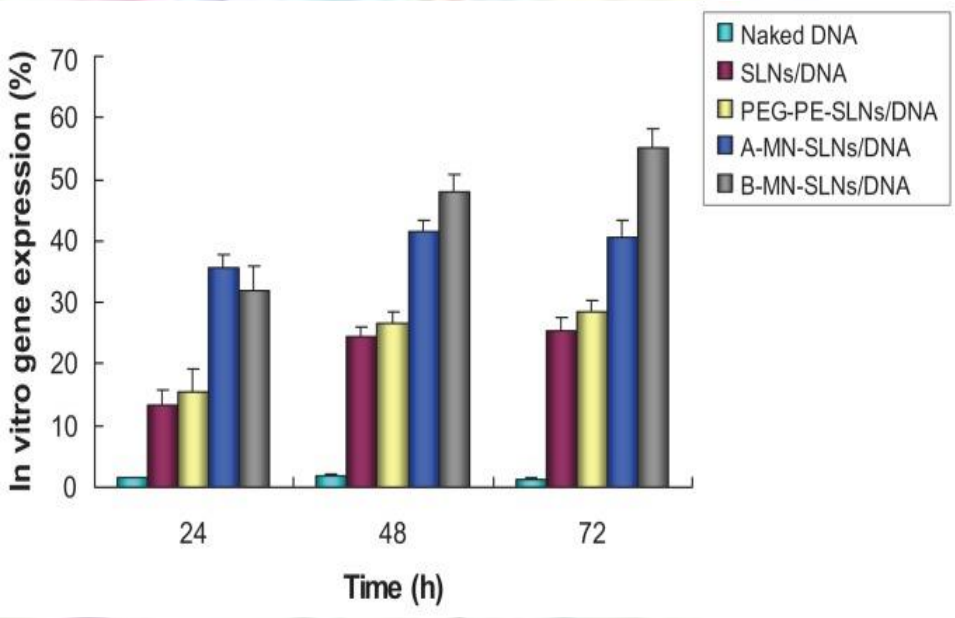
gene therapy[11]*:*

- ***good specificity to target cell***
- ***higher efficacy for transfection of genetic material***
- ***Viral vectors unwanted immune response***
- ***non viral transfection like dendrimers***
  peptide
  cationic lipids
  polymers and liposome

low in-vivo effectiveness

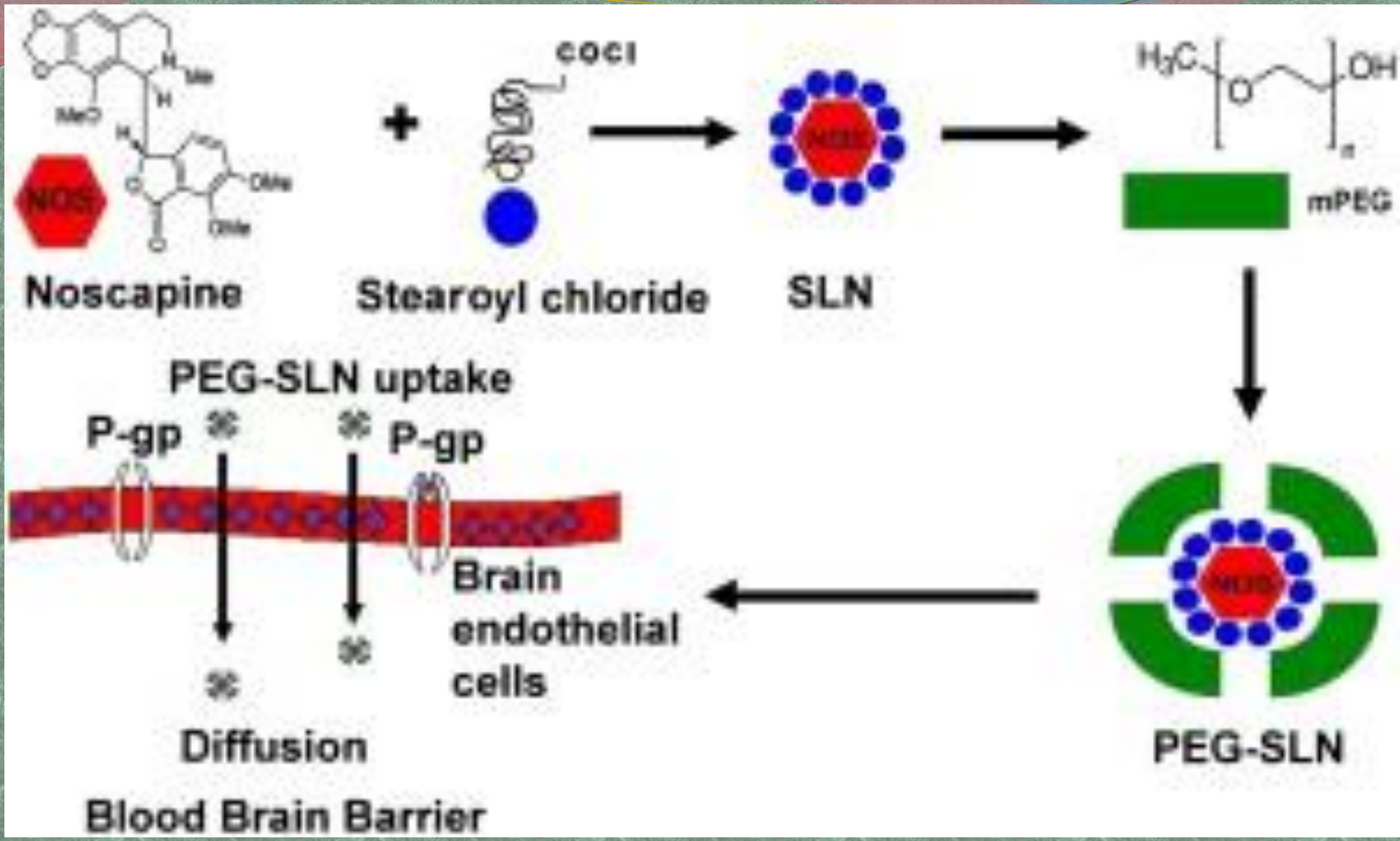
gene therapy:

- *first in-vivo study*
- *Gasco et al evaluated the transfection capacity*
- *SLN-DNA vector in mice.*
- *prevent macrophage uptake*
- *Protein expression for at least one week.*



central nervous system[4]:

- *inability of drugs to pass blood brain barrier (BBB)*
- *SLN: transport of BBB and tissue distribution increase*
- *Fundaro et al, 2000:doxorubicin loaded stealth and non-stealth SLN*
- *stealth nanoparticles in blood at higher concentrations than non-stealth SLN after 24 h*



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Toxicity aspects

- ***Well tolerated***
- ***Metabolic pathway***
- ***Particle size: No problem***

peroral or transdermal administration

and i.m. or s.c. injection

parenteral administration:

pyrogens must be checked

Particle size distribution: embolism

In vivo fate:

- ***(a) administration route***
- ***(b) interactions of the SLN with the biological surroundings:***

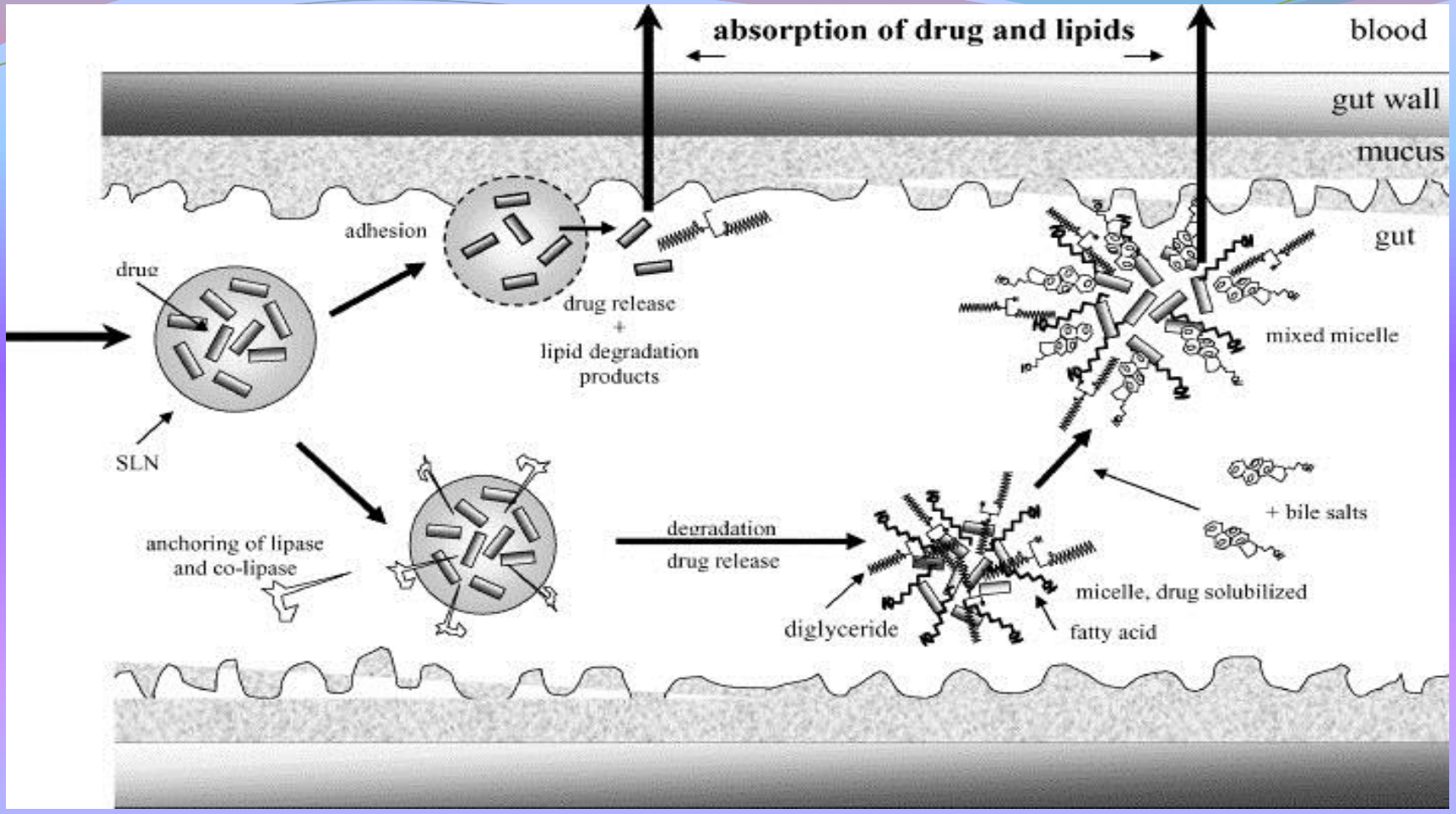
distribution processes:

adsorption of biological material

desorption of The microclimate of SLN component

enzymatic processes:

lipases and esterases



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